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THE MECHANISM OF EVOLUTION[1]

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VI. The Cellular Basis of Evolution

IN sexual reproduction which is well nigh universal among animals and plants adult organisms can give rise to other adult organisms only through the germ cells, and just as the germ cells are the only living bond between generations, so also they are the only living bond between species. Hereditary likeness and specific constancy are due to the persistence of germinal organization; hereditary variation and evolutionary changes are caused by changes in this germinal organization.

1. *Modifications of Cytoplasm*

Of all portions of the germ cells the cytoplasm undergoes the most extreme modifications. The remarkable changes which it passes through in the course of embryonic differentiation have been referred to in preceding pages; but while these changes constitute the sum and substances of individual development they do not affect heredity or evolution. It is certain that the cytoplasmic differentiation of nerve, muscle and gland cells have no direct influence upon the hereditary constitution of the germ cells and it is very doubtful whether the cytoplasmic differentiations of the germ cells themselves affect their hereditary value. The highly differentiated cytoplasm of the spermatozoon has apparently no influence even on the development of the egg which it fertilizes and while differentiations of the cytoplasm of the egg do control some of the most important orientations of development there is no satisfactory evidence that these differentiations are not the result of the environment or of the activity of chromosomes during early stages in the formation of the egg.

The only cytoplasmic modifications or mutations which could be of evolutionary significance would be those which might be transmitted to other generations through the cytoplasm of the germ cells and chiefly through that of the egg cell. One such type of cytoplasmic transmission, which must however have played a very small rôle in evolution, is found in living bodies such as plastids, symbionts or parasites which live and multiply in the cytoplasm and are carried from one generation to another in the cytoplasm of the germ cells.

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[1] William Ellery Hale Lectures before the National Academy of Sciences, Washington, April 16 and 17, 1917.

On the other hand the orientations of the egg cytoplasm initiate and to a large extent determine the character of all the orientations of development and if it could be proved that the polarity, symmetry, or pattern of localization of the cytoplasmic substances of the egg are carried over from generation to generation, modifications of these differentiations would be of profound influence in evolution. I have elsewhere shown that such a marked modification as the total reversal of the symmetry of the body can be traced to a reversal of the symmetry of the cytoplasm in the unsegmented egg and that changes in the orientation of organs and systems such as are found in vertebrates as contrasted with invertebrates can be most readily explained by tracing them back to changes in the localization of formative substances in the cytoplasm of the egg. The problem of the origin of one phylum or type from another has always involved as one of its chief difficulties such changes in orientation and localization and in a previous section we have seen how earlier evolutionists blundered in attempting to explain how one developed animal might be transformed into another by turning it upside down or inside out. Such changes which are utterly impossible in developed organisms might readily be brought about by relatively slight changes in the cytoplasmic localizations of the unsegmented egg.

Furthermore the integrating and coordinating factors in ontogeny and phylogeny are no less important than the differentiating factors; indeed in some regards they may be said to be more important for without these not only development and evolution would be impossible but organisms would cease to be organized and life would cease to exist. At present we know that many of the integrations of development can be traced back to the polarity, symmetry and localization pattern of the egg cytoplasm. If these differentiations and integrations of the cytoplasm are carried over from generation to generation, then modifications of them must be a very important process of evolution. On the other hand if these differentiations arise anew in each egg cell, as do the various differentiations of tissue cells, through the interaction of nucleus, cytoplasm and environment. then evolutionary changes in orientation may find their ultimate causes in changes in the nucleus rather than in the cytoplasm.

Certain changes in polarity, symmetry and localization of formative substances in eggs may be brought about experimentally by subjecting them to strong centrifugal force but such changes are usually of a temporary character and in no instance have subsequent generations been studied to find whether these changes are ever inherited. Lang has shown that inverse symmetry in the snail *Helix pomatia* may occasionally appear in normal dextral stock, but that sinistral parents almost invariably give rise to dextral forms; in general there seems to be no regular rule of inheritance of this character. It may be indeed that inverse symmetry is not inherited at all but is the result of environmental causes.

Therefore in the present state of our knowledge there is not sufficient evidence to conclude that modifications of the cytoplasm of germ cells are ever really inherited or that they are ever the initial steps in evolution.

2. *Modifications of Chromosomes*

We have already considered the evidences that the germinal organization which is primarily concerned in hereditary constancy or variation is found chiefly if not entirely in the chromosomes. Evolution therefore involves the problem of changes in the chromosomes or in the units which make up chromosomes, such as chromomeres and genes. Weismann maintained that germplasm must be in a high degree (*a*) stable, (*b*) distinct, (*c*) continuous. The chromosomal organization is more stable than the cytoplasm which undergoes many changes during ontogeny, while the chromosomes usually remain unchanged. The chromosomes being located within the nucleus and the nucleus within the cell-body are protected from extrinsic influences more than the cytoplasm. Furthermore they are relatively distinct from the cytoplasm and they are continuous from cell to cell and from generation to generation.

Undoubtedly modifications of chromosomal organization may and do take place. Only the grosser modifications can be seen directly, while many others must be inferred from physiological responses such as the results of development. Most of the visible changes which take place in chromosomes occur during mitoses while intermitotic stages are relatively more stable. Slight chemical, thermal or osmotic changes in the medium may produce extraordinary modifications of mitoses, whereas during resting stages changes many times as great may produce no visible or lasting effects. Almost all of the experimentally produced changes in chromosomes which are known to persist occur during mitoses, while those which are produced during intermitoses are, with one or two exceptions, relatively unimportant and temporary. This may be due to the fact that the chromosomes of mitotic stages are bodies which may be counted and in some cases individually identified, whereas during intermitoses it is difficult if not impossible to count or identify them. Since most of the visible modifications of chromosomes are seen as changes in their size, shape or number it is evident that these modifications could be seen only during mitosis. Many of these modifications are due to abnormalities in the division or separation of chromosomes and such abnormalities are necessarily limited to mitotic stages. Of course the chromosomes are not absolutely removed from the influence of external changes at any time but any influences that reach them during resting stages must come through the cell membrane, the cytoplasm and the nuclear membrane, whereas during mitosis the nuclear membrane is lacking. And in addition to this form of protection from external influences the chromosomes are more solid and consequently less easily changed than the surrounding plasma. But the principal reason why chromosomal changes occur during mitosis is to be found in the fact that the movements which accompany mitosis are interfered with so that division or separation of chromosomes does not take place normally.

Changes in resting nuclei due to the volume or quality of the cytoplasm or to chemical or physical changes in the medium are usually of a temporary nature and have no evolutionary significance. Variations in the volumes of chromosomes are dependent upon the volume of the resting nucleus and this upon the volume of fluid cytoplasm. These variations have no hereditary or evolutionary value as is evident from a comparison of the nuclei and chromosomes of ova and spermatozoa which differ greatly in volume but not in value.

Abnormalities in the conjugation (synapsis), separation (reduction) and distribution (equational division) of chromosomes are much more permanent and important. The two former occur only during the growth and maturation of the germ cells;[1] the last named may occur at any stage during the life cycle and in any cells of the organism, but if any abnormality is to affect the next generation it must be found in the "germ track" (germ-cell lineage). It is not surprising that modifications in the constitution or number of chromosomes are peculiarly liable to occur in the maturation stages in view of the fact that during these stages several complex processes occur which are usually lacking in ordinary mitoses. Among these are (*a*) synapsis or the union of homologous chromosomes from the two parents into pairs, the subsequent splitting of each member of a pair and the condensation of the four "chromatids" thus formed into one "tetrad" (Fig. 12, p. 274); (*b*) reduction or

[1] Metz has found that maternal and paternal chromosomes are paired in every mitosis in *Drosophila* and some other insects.

the separation of whole chromosomes of each pair and their movement to either pole of the mitotic figure (Fig. 17, p. 283); (*c*) the occurrence of two maturation divisions without the intervention of a resting stage by which the four "chromatids" of each tetrad are distributed to four different cells (Fig. 22, p. 389). As a matter of fact most of the persistent modifications of chromosomes which have been discovered hitherto appear during maturation stages.

(*a*) *Changes in Chromosome Number.*—The typical chromosome number may be more or less permanently changed and the developed organism may be greatly modified by non-disjunction of synapsed chromosomes, as Bridges has demonstrated (see p. 287). Probably many other cases in which the number of chromosomes and the characters of the developed organism are atypical may be caused by non-disjunction. For example it is known that *Œnothera lamarckiana* has typically 14 chromosomes in the zygote and 7 in the gametes, but the mutants *O. lata* and *O. scintillans* have 15 chromosomes (Gates, Lutz); the half-mutant, *O. semigigas,* has 21 chromosomes (Stomps), while the mutant, *O. gigas* has 28 (Gates). A likely explanation of the condition found in *lata* is that non-disjunction occurred in one pair of chromosomes of one gamete, whereas in *semigigas* it occurred in all the pairs of one gamete, and in *gigas* in all pairs of both gametes, and in this connection it is significant that *lata* has appeared many times, *semigigas* several times and *gigas* but twice.

Similar modifications of the typical number of chromosomes have been found in a considerable number of plants and animals. For example in *Ascaris megalocephala,* var. *univalens* there is 1 chromosome in each gamete and 2 in the zygote; in var. *bivalens,* which is otherwise indistinguishable from *univalens,* there are 2 in each gamete and 4 in the zygote. A similar case occurs in the sea-urchin *Echinus microtuberculatus* where 18 chromosomes are found in some individuals and 36 in others. The reduced number of chromosomes in a gamete is the *haploid* number; the usual number in a zygote is *diploid;* if an unreduced gamete and a reduced one conjugate the number is *triploid;* if two unreduced gametes unite the number is *tetraploid.* The triploid and tetraploid numbers are probably due to non-disjunction of all the chromosome pairs of one or of both gametes at the reduction division or to the failure of all the daughter chromosomes to separate in some of the ordinary divisions of the germ track. Both triploidy and tetraploidy have been repeatedly seen in many different plants and animals and in general they lead to gigantism, not only the entire organism being larger than normal but also the individual cells and nuclei.

It is well known that unusual chromosome numbers may result from hybridization of two forms having an unequal number of chromosomes. Thus Herla found that when the two varieties of *Ascaris megalocephala* were crossed, *univalens* having one chromosome in each gamete and *bivalens* two, the hybrid had three; and in all cases of hybrids the number of chromosomes in the zygote is the sum of those present in the two gametes. The same is true when more than one spermatozoon fertilizes an egg. Thus Boveri found that 54 chromosomes are present in a doubly fertilized sea-urchin egg, when each of the gametes contains 18 chromosomes. But since each spermatozoon brings into the egg a centrosome which quickly divides into two there is usually formed a four-poled spindle (tetraster) and the daughter chromosomes are distributed unequally to these four poles and to the four cells into which the egg divides. In general he found that those cells which contained a full haploid set of chromosomes developed normally while those which received less than a full set developed abnormally.

Spindles with three or four poles (triasters, tetrasters) and with double the normal number of chromosomes may result from the failure of the cell-body to divide following the mitotic division of the nucleus, and if centrosomes and chromosomes continue to divide while the cell-body remains undivided a great number of centrosomes (polyasters) and of chromosomes may be found in one cell. Whenever more than two centrosomes are present the chromosomes are almost certain to be unequally distributed to the poles of the mitotic figure, and to the daughter cells if the cell-body divides. Sometimes chromosomes are scattered along the mitotic spindle and do not move to its poles, so that when the daughter nuclei are formed these scattered chromosomes are left out in the cell and are ultimately lost. In all of these cases irregularities in the number of chromosomes are due to abnormalities of the mitotic apparatus by which the separation of daughter chromosomes is effected.

On the other hand variations in the number of chromosomes are not always due to non-disjunction at the reduction division nor to the failure of daughter chromosomes to separate in ordinary mitoses, as is shown by the fragmentation of the chromosomes of somatic cells in Ascaris, the pig and in *Œnothera scintillans* (Hance, p. 395), and also by the fusion of chromosomes into compound ones called by McClung "hexads," "decads," etc., as in some insects. In these cases it is certain that the unusual numbers are not due to non-disjunction but rather to a fragmentation or to a fusion of chromosomes. Metz has found that in different species of *Drosophila* the number of chromosomes varies from 6 to 12 depending, apparently, upon fragmentation or fusion of original chromosomes. In cases of fragmentation or fusion of chromosomes the quantity of chromatin and presumably the number of chromomeres remains the same. Consequently changes in the number of chromosomes caused by fragmentation or fusion represent merely changes in the grouping of chromomeres and not changes in the constitution of the hereditary material.

Abnormalities in the distribution of chromosomes of a cell persist in all its daughter cells and are not usually corrected. On the other hand abnormalities in the distribution of cytoplasmic substances to the cleavage cells frequently occur and usually the cell returns to a normal condition by a process of regulation. But when once the normal number of chromosomes has been changed there is no regular means of restoring that number. Momentary changes in the temperature, density or chemical composition of the medium may thus produce permanent changes in the distribution of chromosomes and of germplasm. Such changes in the distribution and number of chromosomes are usually of so gross a character that the development is not only very abnormal but also the resulting organism is incapable of continued life and reproduction. Consequently such changes do not usually give rise to new races or species; only in the most favorable cases where at least the full set of haploid chromosomes is present does the new form survive and reproduce.

Although abnormality in chromosome number is found in some mutants it is by no means certain that this abnormal number is the cause of mutation and there are some good evidences that it is not. For example, deVries finds that the tetraploid number in *Œnothera lamarckiana,* mut. *gigas* is a result rather than a cause of this mutation. *Gigas* is not merely a tetraploid *O. lamarckiana* but a true mutation in which the tetraploid number of chromosomes is one of the new characters. Stomps confirms this conclusion of deVries; he finds in *O. lamarckiana* and in *Narcissus poeticus* that the *gigas* condition may occur with or without doubling of the chromosomes; Gregory has found the same thing in *Primula sinensis.* Therefore in those *gigas* mutants in which the number of chromosomes is doubled we can not conclude that this is the cause of the mutation.

A similar condition is found in those animals in which the male has one less chromosome than the female; it has sometimes been assumed that the sex is caused by the number of chromosomes, and yet in many species the male and female have the same number, the sex chromosomes in one case being known as *XY* and in the other as *XX*. Morgan and his co-workers have shown that it is not the *number* of chromosomes which determines sex but the *kind* of chromosomes. This case bears directly upon the supposed relation between chromosome number and evolution, for the differences between a male and a female of the same species are frequently as great as those between two different species; indeed males and females might be regarded as mutants, were it not for the fact that both forms recur in every generation because of the recurrence of male and female chromosome combinations.

(*b*) *Changes in Chromosome Constitution.*—But just as sex differences are not always associated with a difference in the number of chromosomes, but often with differences in size or constitution of particular chromosomes, so mutants do not always nor even usually have different *numbers* of chromosomes though particular chromosomes probably differ in quality in different cases. Janssens discovered that chromosomes of a synaptic pair may twist around each other and he inferred that when they separate in the reduction division sections of the two may have interchanged places. Robertson and Wenrich have described a more complicated form of "crossing-over" due to a longitudinal splitting of each chromosome of a synaptic pair, the condensation of these four chromosomes into a tetrad and the subsequent separation of these in such a way that chromosomal interchange takes place. Morgan and his associates have shown that many important changes in the linkage of characters which are inherited in groups may be explained by this "crossing-over" of sections of homologous chromosomes (see p. 289).

But changes in chromosomal constitution are rarely directly visible, although they may be inferred from the results of development. By the study of Mendelian ratios Shull has shown that in certain cases a particular gene is duplicated in certain gametes. He points out that such "duplicate genes" could be caused by the synapsis of non-homologous chromosomes or by the transfer of part of one chromosome containing such a gene to another non-homologous one. In the former case the chromosomal grouping would be changed so that each gamete would contain two homologous chromosomes; according to his second hypothesis the *constitution* of two chromosomes would be modified, namely the one from which the gene in question was removed and the one to which it became attached. Bridges also has shown that there is genetical evidence that sections of one chromosome may in some cases be joined to another non-homologous one, and the cytological evidence shows that in certain cases chromosomes undergo fragmentations, in other fusions, and that a chromosome is not invariably composed of the same chromomeres. Bridges has described a phenomenon in *Drosophila* which he calls "deficiency" and which consists in the elimination (or inactivity) of certain closely linked genes, probably as the result of the dropping out (or the inactivation) of a section of a chromosome.

(*c*) *Experimental Modification of Chromosomes.*—Experiments on dividing cells show that chromosomes, like all forms of protoplasm, may be modified, injured or destroyed by various chemical substances, by increasing or decreasing the density of the surrounding medium, by increasing the temperature slightly above the optimum, by an electric current, X-rays, radium, etc. Such experimental conditions also cause very abnormal separation and distribution of the chromosomes in mitosis.

Such modifications of chromosomes either stop development altogether or they produce profound monstrosities which usually bring development to an end at an early stage. In few if any cases has it been possible to carry such abnormal forms to maturity and in no instance has any one been able to study the effects of such modifications of chromosomes on subsequent generations. Evidently experimentally produced modifications of chromosomes which are large enough to be visible with the microscope are usually too great to allow of their being carried over to another generation. However Plough has found that high temperature acting on the early oocyte stage of *Drosophila* increases the number of cross-overs and of course such changes are transmitted to subsequent generations; here is indirect evidence of the fact that the constitution of chromosomes may be modified and direct evidence that genetical constitution may be changed by environmental influences acting on the germ cells at an early stage. Probably many other changes in the constitution of chromosomes may be traced to environmental influences; if so initial stages in evolution may find their causes in such influences.

3. *Changes in Genes*

Although some inherited variations are caused by changes in whole chromosomes or visible portions of chromosomes, by far the larger number of such variations show no such visible causes. Nevertheless there is evidence that such variations are caused by changes in invisible units or genes which are located in the chromosomes. Reasoning from the seen to the unseen, from chromosomes to genes, we are justified in concluding that the behavior of the two is comparable, except that in general the simpler a unit is the more stable it is. Chromosomes are more stable than cytoplasm but genes are probably much more stable than chromosomes. We have seen that chromosomal organization may be modified: (1) by changes in number or combination due to the omission or addition of whole chromosomes, (2) by changes in constitution due to new combinations of the parts of which chromosomes are composed. It seems probable that genes also may be modified in these two ways.

(*a*) *New Combinations vs. New Constitution of Genes.*—The genetical evidence proves that entire genes may be transferred from one chromosome to another as in "cross-overs" or "duplicate genes" and that entire genes may be lost or rendered inactive as in "deficiency." In this way new combinations of genes are formed which lead to important changes in heredity and development and which may become initial stages in evolution. Furthermore it is highly probable that individual genes, in some cases, undergo a change in constitution owing presumably to fragmentation or new combination of the parts of which they are composed. In this connection it is interesting to recall that Darwin recognized two kinds of variations, (*a*) those caused by changes in the number of pangenes and (*b*) those caused by changes in the pangenes themselves ("Variations," Vol. II., p. 390). DeVries also made this distinction at an early date, in his "Intracellular Pangenesis" (pp. 73, 210). In the conception of deVries either of these changes are mutations; on the other hand Morgan and his school look upon mutations as changes in the constitution of individual genes, while new combinations of genes are not regarded as mutations in a strict sense.

The most important work on mutations and their causes has been done by deVries on the evening primrose, *Œnothera lamarckiana,* and by Morgan on the pomace fly, *Drosophila melanogaster.* In the former more than a score of mutants have been discovered and studied genetically, since 1900, in the latter more than 150 since 1910. Several geneticists, notably Johannsen, Heribert-Nilssen, Lotsy, Davis and Bateson, maintain that there is no sufficient evidence that *Œnothera lamarckiana* is a homozygous or pure form and they hold that the mutations described by deVries are the results of Mendelian segregation from this impure stock. This conclusion has now been demonstrated by Shull in the most satisfactory manner. The fact that such mutations occur only rarely and that they do not exhibit Mendelian ratios may be explained by the partial or complete sterility of certain gametes or zygotes, for in this genus there is much sterile pollen and many seeds fail to germinate. In *Drosophila* a large number of lethal factors have been discovered which cause the early death of zygotes in which they are not balanced by normal factors. In *Œnothera* also such lethals probably cause the death of certain classes of gametes and, if only those gametes which are different in the two sexes survive, the species will remain constantly heterozygous. In such a case if certain recessive factors are linked in the same chromosome with lethal ones they could come to expression only when by crossing-over this linkage was broken, and it seems probable, as Muller has said, that many mutants of *Œnothera* "are merely the emergence into a state of homozygosis, through crossing-over, of recessive factors constantly present in the heterozygous stock." Of the nine mutants of *O. lamarckiana* which were first discovered by deVries no less than five (viz., *lævifolia, albida, oblonga, rubrinervis* and *nanella*) are probably due to such cross-overs; three are possibly due to alterations in the usual number of chromosomes (viz., *lata, scintillans* and *gigas*) though the most recent work indicates that this is not the real cause of these mutations; while one (*brevistylis*) is evidently due to a change in a particular gene. If this interpretation is correct the *development* or appearance of all of these mutants depends upon a particular combination of dominant or recessive genes, though only in the last named mutant does this follow the rule of simple Mendelian segregation. But granting all this we explain only the peculiar manner of *segregation* of dominant and recessive factors in *Œnothera* and we find no explanation of the *origin* of such factors; the real problem after all is to explain how a dominant factor may give rise to a recessive one or *vice versa.* Here it seems logically necessary to assume that the individual factor undergoes some chemical or physical change. Peculiar combinations of dominant and recessive genes will explain the development of such mutants but not the origin of peculiar genes.

(*b*) *The Dogma of Immutable Genes.*—It is known that genes are relatively very stable; they may be carried along unchanged through hundreds of generations and thousands of individuals. Morgan calculates that there must be at least 7,500 genes in *Drosophila melanogaster* and yet in some hundreds of generations and many thousands of individuals he has found only about 150 mutant types although *Drosophila* seems to be mutating more rapidly than most species. The constancy of some species can be measured not only in years but even in geological ages and the constancy of some characters must be greater than that of a species, while the constancy of genes in general must be even greater than that of characters.

This relative stability has given rise to a dogma that genes are immutable and that all changes in the material basis of heredity are caused by new combinations of the same old genes; Lotsy in particular holds this view. It is interesting from the historical standpoint to recall that immutability has been ascribed to (1) species (Linnæus), (2) elementary species (Jordan), (3) pure lines (Lotsy), (4) unit characters (deVries), (5) germplasm (Weismann's earlier work), (6) genes (Lotsy). Immutability, like spontaneous generation, has sought refuge successively in smaller and smaller units but there is no reason to suppose that these smallest units of living matter are changeless. Indeed neither molecules nor atoms are now supposed to be absolutely changeless. In general the stability of any unit is proportional to its simplicity; no units of living matter are absolutely simple and therefore none is absolutely stable.

We know that species, subspecies, pure lines, persons, cells, chromosomes are subject to change. Genes are at the least very complex molecules and it is incredible that they are immutable or absolutely removed from influences of external or internal environment. The dogma of immutable genes leads logically to the position taken by Lotsy, namely, that there is no real variation, no actual evolution, no genuine progress; in short to a philosophical system of negations which is contrary to experience both in its assumptions and conclusions.

What are Genes?—As long as these units are not identified as material bodies it is possible to invest them with all the properties we are trying to explain and thus to shift the problems of heredity and evolution to a more inaccessible field. To a certain extent this has been done by Weismann and his followers. In all cases an "explanation" must be in more general terms than the thing to be explained.

Undoubtedly genes are material bodies with chemical and physical properties. Undoubtedly they are capable of growth and division like any other living units, though it is possible that they are not living in a strict sense. Their method of growth and division indicates that they are more than single molecules and are probably colloidal aggregates of molecules, though their great stability led Morgan at one time (1917) to suggest that they might be single molecules. The fact that they have the power of growth and division suggests that they are autocatalytic substances (p. 276) and their great influence on development in spite of their very small size, as well as their specificity, has suggested to several writers that they are enzymes or bodies which produce enzymes.

(*c*) *Mutation of Genes.*—The fact that genes are relatively complex bodies would indicate that they can not be absolutely stable and wholly uninfluenced by environment, for nothing can be such which is not absolutely simple. Assuming then that genes are at least very complex molecules of protein-like substance and that more probably they are colloidal aggregates of such molecules, we may conclude that they undergo change by dissociation and recombination of the molecules, radicals or atoms of which they are composed. With large and complex molecules enormous numbers of different combinations of the same atoms are possible; thus Miescher calculates that a molecule of albumin with 40 carbon atoms may have as many as one billion stereo-isomers, and in protoplasm there are many kinds of albumin and other proteins, some with more than 700 carbon atoms. Reichert says that serum albumin may theoretically exist in as many as a thousand million forms. Therefore, even if genes are single molecules, it is chemically possible to have an enormous number of variants of each of them, and if they are aggregates of such molecules the number of different kinds which would be chemically possible would be greatly increased. Mutation in genes may therefore be thought of as due to the loss or addition of certain constituent atoms or molecules or to the rearrangement of some of these. But on the other hand the fact that genes are relatively very stable indicates that something other than the possibilities of chemical alteration are involved in their mutations.

It is an interesting fact that many mutations seem to involve the loss of something; very many if not the majority of the mutations which have occurred among domestic animals and cultivated plants are of this sort, such as the loss of color (albinism) in many plants and animals, the loss of glumes or bristles or hairs, etc. Such mutations deVries calls "regressive." On the other hand a few mutations seem to add something which was not present before and these deVries calls "progressive" and he thinks that they are of especial significance in evolution. We must not however conclude that the loss or addition of a character means the loss or addition of a new gene nor even of molecules or atoms of a gene, for the rearrangement of the parts of a gene may lead to the appearance of new characters just as the rearrangement of the atoms of a molecule may lead to new qualities in a chemical substance. The old idea of evolution by addition of new characters, or by accretion, is out of harmony with what we know of individual development where differentiation takes place by the transformation of units already present and not by additions of new units. Nowhere in the entire process of organic evolution is there any evidence that new genes are "extrinsic additions" or are created *de novo*. When Morgan says: "Evolution consists largely in introducing new factors that influence characters already present" (1917) he can only mean that new combinations of the same old genes are brought about by crossovers, non-disjunction or fertilization, or that new kinds of genes arise by transmutation of old ones through new combinations of the elements of which genes are composed. The whole mechanism of evolution consists in new combinations of the units of organization whether those units be characters, cells, chromosomes, chromomeres, genes, subgenes, molecules or atoms.

Mutants are in the main recessives when mated with their normal allelomorphs, but they are not always recessive as is claimed by Lotsy. Among more than 150 mutants which have appeared in Morgan's cultures of *Drosophila* 12 are dominant or semi-dominant. Many other dominant mutants are known such as abnormally short limbs, fingers and toes, supernumerary digits, hereditary cataract and other eye defects in man, hornlessness in cattle, rumplessness in poultry, red sunflowers, red buds in *Œnothera lamarckiana, mut, rubricalyx, et al.*

Morgan and his school have proved by genetical evidence that a particular gene may change in any one of several different ways, probably owing to various changes in its composition. Thus the gene for the normal red eye color may change so as to give rise to "blood," "cherry," "eosin," "buff," "tinged" or "white" eyes. Genes, or allelomorphs, that mutate in various directions give rise to what are known as "multiple allelomorphs"; hypothetically these may be explained as due to different changes, probably of a chemical nature, in a particular gene. Not only may genes mutate in different directions but some genes apparently mutate more frequently than others, as Emerson has shown in the case of corn and as Morgan has found in *Drosophila*. DeVries especially has long maintained that some genes are more "labile" than others, although more recent work on *Œnothera* indicates that this so-called lability may be caused by crossing-over, at least in some instances.

Furthermore the same mutation may occur independently in different cultures or even in different species. Thus Morgan says that white eyes have appeared independently in his cultures of *Drosophila* three different times, vermilion eyes six times, rudimentary wings five times, etc. In this case it is known that the mutating gene in each instance named occupies the same locus in the chromosomes and there can be no doubt that each of these recurring mutations is due to the same sort of change in the same gene. DeVries has observed the independent recurrence of the same mutation in different cultures of *Œnothera,* and other investigators have noted a similar phenomenon in other organisms; these are probably caused by identical changes in particular genes. The independent recurrence of a mutation must indicate a tendency for a gene to change in a particular way just as chemical changes tend to go in certain directions. A similar cause probably underlies the tendency of organisms to evolve in definite directions—a phenomenon which has been called "orthogenesis" (Haacke, Eimer, Whitman) and which has been especially emphasized by paleontologists.

Not only do the same mutations recur within the same species but apparently identical mutations may appear within different species. Metz has shown that certain mutants of *Drosophila virilis* closely resemble corresponding ones in *D. melanogaster* and that in both species the mutating genes are located in corresponding chromosomes; however such cases are exceptional. Albinism, melanism, gigantism, etc., have appeared repeatedly in many different species, and this raises the interesting question whether identical genes may occur in different species and undergo identical changes. While this may be true in some cases it is certainly not true in all. Mutations which look alike may be genetically different; albinism, for example, is recessive in mammals while at least two kinds of albinism occur in poultry, one of which is dominant and the other recessive. White flowers even within the same species may be due to mutations in different genes, as in the case of sweet peas; Morgan has shown that mutants of *Drosophila* which look alike may be caused by mutations of different genes, occupying different loci in the chromosomes. We can not conclude, therefore, that mutations which look alike are always due to similar changes in identical genes.

Mutations of genes may probably occur in any cell, but if they are to be transmitted to the next generation by sexual reproduction they must take place in the germ-cell lineage at least as early as the maturation stages in the case of dominant or sex-linked characters and possibly much earlier, while in the case of recessive mutations they may occur many generations back and be carried along without giving any sign of their presence until they are mated with a similar recessive mutaiton. In such cases the actual mutation occurs long before it comes to expression in a developed mutant.

(*d*) *Extrinsic Causes of Mutation.*—Various changes in the chemical and physical environment produce abnormalities in the number, distribution and constitution of chromosomes, as was pointed out on a previous page, and it is not antecedently improbable that such environmental changes may produce similar modifications in genes themselves. Nevertheless it must be admitted that at the present time no single case is known in which such environmental changes have certainly produced a mutation in a gene.

Several investigators have described cases in which mutations have been ascribed to the action of external agencies, but in no one of these cases is it certain that the external change produced the mutation in question. One of the first instances of the supposed experimental production of a mutation was described by MacDougal in 1905. He reported that he had injected various solutions, particularly zinc sulphate in different concentrations, into the ovaries of a species of *Œnothera* (*Raimannia*) and had obtained as many as 13 different mutants. A year later he reported that he obtained 3 mutants in a similar way. These results have not been confirmed by other workers and the evidence seems to favor the view that MacDougal was dealing with a naturally mutating stock and that the mutants were not caused by the experimental conditions.

Tower (1906) carried on extensive and prolonged studies on the evolution of the potato beetle, *Leptinotarsa*, and concluded that he had induced mutations in this form by changes in humidity and temperature acting upon the germ cells at a sensitive stage in their genesis, presumably by causing mutations in the genes. But in this case also it is not certain that the mutations observed were actually caused by the experimental treatment and there are many reasons for concluding that they were not.

Many other investigators have studied the injurious effects on development of different experimental conditions acting on the germ cells. Thus Bardeen and O. Hertwig found that when normal frog's eggs were fertilized by spermatozoa which had been exposed to X-rays or radium the resulting development was very abnormal. Cole found that when lead acetate was fed to rabbits or fowls their germ cells were so affected that they produced abnormal offspring. However in none of these experiments is it known that these abnormalities were heritable, since they were not followed to later generations.

Stockard has made an extensive study of the inherited effects of alcohol upon guinea pigs. He finds that the offspring of alcoholized animals are frequently weak and abnormal and that these effects may be traced to the third or fourth fillial generation. The effects of alcohol on the male germ cells seems to be greater than on the egg cells, and since the portion of the spermatozoon which enters and fertilizes the egg is composed almost entirely of chromosomes it seems reasonable to conclude that the chromosomes have been injured by the alcohol. On the other hand there is no evidence here that individual genes have been caused to mutate and the fact that the injurious effects wear off after three or four generations seems to indicate that the changes produced by the alcohol are not of the nature of mutations. It should be said that Pearl's experiments on the inherited effects of alcohol on chickens do not support Stockard's results; he finds that the offspring of alcoholic parents are fewer in number but stronger than those from normal parents and he concludes that the effect of the alcohol is to kill the weaker germ cells and embryos and to permit only the more hardy ones to survive.

In these experiments with alcohol there is no evidence that genes have been caused to mutate, and indeed there is no satisfactory evidence that the defects observed in the offspring of alcoholic guinea pigs were really inherited. It is known that many environmental influences, such as food, temperature, soil, etc., may modify the development of the first and even the second succeeding generation and then disappear, as Whitney has shown in the case of Rotifers, Woltereck in *Daphnia* and Harris in beans. Such temporary modifications are not really inherited and are known as "induction" phenomena. They do not represent modifications in heredity but rather in development, not mutations in genes but possibly alterations of the cytoplasm.

In conclusion it may be said that although it is certain that mutations of genes take place and although it is highly probable that these mutations, like all chemical and physiological processes, are affected by environmental conditions, nevertheless we do not know what the conditions are which induce mutations and at present we are unable to initiate or control them.

(*e*) *Intrinsic Causes of Mutation.*—The failure to find definite extrinsic causes of mutation has led certain students of the subject to conclude that all changes in genes are due to intrinsic causes. The gene has been compared to the radium atom which undergoes disintegration wholly uninfluenced by temperature or other physical or chemical conditions. But, as has been indicated, the gene is not an atom but at the very least an extremely complex molecule and it is incredible that it should be wholly removed from environmental influences, since this is true of no other molecule or group of molecules.

We have no more direct knowledge regarding the intrinsic causes of mutation than concerning the extrinsic ones and yet we may safely assume that certain general principles which apply to visible portions of the organism are true of invisible genes. As development or any physiological process is the response of an organism to various stimuli, so we may assume that mutations also represent the response of the hereditary organization to certain stimuli; and just as the nature of any response is primarily determined by the nature of the organism while the stimuli serve merely to initiate, hasten or retard the response, so the nature of a mutation is probably definitely limited by the organization of the germplasm while its extrinsic causes serve only to initiate or retard it. With true insight Charles Darwin wrote many years ago:

> Although every variation is either directly or indirectly caused by some change in the surrounding conditions, we must never forget that the nature of the organization which is acted on essentially governs the result.

Some conceivable mutations never become real because of these intrinsic limitations. "Whales never produce feathers, nor birds whale bone," said Huxley; and probably no one ever really saw a green horse or a purple cow.

Mutations can not therefore take place in all conceivable directions, owing to the limitations of the organization of the germplasm and these same limitations may sometimes cause mutations to follow more or less closely in particular lines, as for example in the independent recurrence of the same mutation, but on the other hand the organization of a gene is so complex that it may undergo many different alterations, as is shown in cases of "multiple allelomorphism." There is no justification therefore for extreme views of orthogenesis which regard mutations as taking place only in a single direction.

Another hypothesis which is the result of a too extreme insistence on the intrinsic factor of mutation is found in the view that all mutations of genes are in the nature of losses or disintegrations more or less comparable to the disintegrations of the radium atom. The "presence and absence" hypothesis assumed that dominant characters are due to the presence of a factor and recessive character to its absence, and since regressive mutations, in which some dominant character becomes recessive, are much more numerous than progressive ones, it was suggested by Shull, Bateson and Davenport that evolution might be due to the loss or disintegration of factors or genes. "This conception results," said Shull (1907), "in an interesting paradox, namely the production of a new character by the loss of an old unit," and he suggests that at least the later stages of evolution may be a process of analysis due to the disappearance of one unit after another. Bateson (1914) also proposed the same thing in his well-known inquiry "whether the course of evolution can at all reasonably be represented as an unpacking of an original complex, which contained within itself the whole range of diversity which living things present"; and in the same category is the speculation by Davenport that "the foundations of the organic world were laid when a tremendously complex molecule, capable of splitting up into a vast number of simpler molecules, was evolved." But the speculation that a recessive character is due to the absence of a factor has been disproved by work on multiple allelemorphs for here although there may be several kinds of recessives to the same dominant allelemorph there can be only one kind of absence. Furthermore this hypothesis of evolution by degredation offers no real explanation of evolution, but like the old doctrine of preformation it merely puts the mystery back into the supposed causes.

But apart from the fact that this hypothesis of evolution by disintegration offers no real explanation of evolution, it does not at all conform with what we know of other natural phenomena. In the inorganic world, as well as in the organic, changes involve not merely breaking down but also building up, not merely analysis but also synthesis. Everywhere in the living as well as in the lifeless world disintegration is balanced by reintegration. Chemical changes are the results not only of dissociation but also of recombination. In embryonic differentiation new structures and functions arise not merely by a process of disintegration of the structures and functions of the egg and a sorting out of these fragments to different cells, but also by the transformation of the germinal structures and functions into those of the developed organism by a process of recombination or "creative synthesis." Similarly in phylogeny new types, new characters, new genes, arise by the transformation of those already present by a process which may be called "creative evolution."

In conclusion we find that it is impossible to avoid the conviction that the initial stages in evolution are caused by new combinations of chromosomes, chromomeres, genes or subgenes, and that these new combinations take place in response to stimuli from the external or internal environment. Probably experimental cytologists have already made many such new combinations which might have given rise to new species, genera or even phyla if they could have survived. Unfortunately almost all of these changes in the germplasm have been of so gross a character that the new forms were unable to live beyond the early stages of development, and the more extreme they were the earlier they perished. Germ cells are so complex and are so delicately adjusted and balanced that they can not usually be greatly changed without rendering them incapable of continued life. Experimentalists have aimed to produce changes in germ cells or embryos which could be seen with the microscope, but it will be necessary to produce smaller and more subtle changes in the germplasm if we are to determine their effects on succeeding generations. The future may show us methods of modifying the germplasm, more delicate and effective than any that have been discovered as yet, and when that time comes, if it ever comes, a real experimental evolution will be possible.

The mystery of mysteries in evolution is how germplasm ever became so complex as it is, so well adapted to give rise to viable organisms, so filled with the marvellous potencies of development. The greatest problem which confronts us is no longer the mechanism of evolution but the evolution of this mechanism. This problem has been shifted from the developed organism to the germplasm, but has not been solved.